REMARKS/ARGUMENTS

Reconsideration of the above-identified application is respectfully requested.

Election of Species

Initially, it is noted that the election of species has been withdrawn and a new one given, *to wit*:

(A) a telomere damage-inducing agent that is (A1) paclitaxel or a derivative thereof: (A2) platinum-based agents, such as cisplatin or carboplatin; or (A3) an agent other than (A1) or (A2);

(B) a telomerase inhibitory agent that is (B1) a nucleoside or nucleotide analog, such as, AZT or d4T; (B2) an antisense nucleic acid; or (B3) an agent that is neither (B1) or (B2),

wherein each patentably distinct species has a distinct telomere damage-inducing agent (A2, A2, or A3) and a distinct telomerase inhibitory agent (B1, B2, or B3).

Applicants hereby confirm their provisional election to prosecute telomere damage-inducing agent (A1) and telomerase inhibitory agent (B1), with traverse. These claims include: 1-24, 26-28, 33-35, 40-47, and newly added 90-92.

Summary of the Invention

The present invention is based on the discovery that paclitaxel treatment of a cancer causes telomere damage, thereby inducing telomerase activity and leading to resistance to paclitaxel treatment. Applicants also discovered that other cytotoxic agents, such as cisplatin, radiation, hyperthermia, and serum starvation, induce telomerase activity. Applicants further discovered that combining paclitaxel with a telomerase inhibitory agent, such as 3'-azido-deoxythymidine (AZT) or 2',3'-didehydro-3'deoxythymidine (d4T), results in synergy. These discoveries have led to the present invention for using combinations of an agent, such as paclitaxel, that causes telomere damage and an agent that inhibits telomerase, such as AZT, d4T, or antisense to the RNA component of human telomerase. Applicants further discovered that the AZT doses used to enhance the antitumor activity of paclitaxel are about 20-fold lower compared to the AZT doses used in the prior art. Similarly, the AZT concentrations needed to enhance the paclitaxel activity are at least several folds lower than the AZT concentrations needed to produce 50% inhibition of telomerase activity as shown in the prior art. Applicants further defined the AZT and d4T concentrations and the AZT doses that produce the greatest synergy with paclitaxel, whereas the prior art does not provide such enabling steps.

Claim Rejections

Claims 24, 26, 27, 45-47 have been amended to correct the typographical errors in the word "nucleotide" to the word "nucleoside", and to correct the typographical error of "dT4" to "d4T". No new matter is added by virtue of these claim amendments. Moreover, such claim amendments are ministerial in nature as they relate to inadvertent errors that are typographical in nature. Accordingly, Applicants assert that no claims have been narrowed with the meaning of *Festo* (*Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 US 722, 112 S.Ct. 1831, 152 L.Ed.2d 944, 62 USPQ2d 1705 (2002)). See also *Interactive Pictures Corp. v. Infinite Pictures Inc.*, Fed Cir., No. 01-1029, December 20, 2001 (addition of the words "transform calculation" was not a narrowing amendment because that addition did nothing more than make express what had been implicit in the claim as originally worded).

The remaining claim amendments will be discussed in connection with the rejections of the claims discussed below.

Claims 1-24, 26-28, 33-35, and 40-47 stand rejected to under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the reduction of telomere length and treatment of cancer related to human breast MCF-7 cells, pharynx FaDu cells, prostate PC3 cells, and ovarian SKOV3 cells, does not provide enablement for inhibiting or reducing the growth of all types of cells or for treating all types of cancer. The Examiner cites the reasons being that undue experimentation is required and the unpredictability in the art. Initially, Applicants would remind the Examiner that working examples in the above-identified application include four tumor models, representing major types of human cancer, including FaDu, which is a head and neck cancer; PC3, which is a prostate cancer; SKOV-3, which is an ovarian cancer; and MCF-7, which is a breast cancer. Together, these cancer types account for about 50% of all adult human cancers. Furthermore, telomerase is expressed in 85-90% of human cancer cells, but not in normal somatic cells and telomerase is required for telomere maintenance, according to published information (see Declaration of Dr. Jessie L.-S. Au, Ph.D.). Based on this data and published information, it is Dr. Au's expert opinion that the invention is likely to also work with other cell types (*e.g.*, cancers) based on her and her co-worker's work to date. This data and expert opinion counter this claim rejection. Thus, its withdrawal respectfully is requested.

Claims 1-24, 28, 33-35, and 40-45 stand objected to under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the reduction of telomere length and treatment of cancer related to human breast MCF-7 cells, pharynx FaDu cells, prostate PC3 cells, and ovarian SKOV3 cells, using a combination of paclitaxel and AZT or d4T, does not provide enablement for inhibiting or reducing the growth of all types of cells or for treating all

types of cancer, nor provide enablement for inhibiting or reducing the growth of a cell or for treating cancer using a combination of paclitaxel and a nucleoside or nucleotide analogue other than AZT or d4T. The Examiner states that not all nucleoside or nucleotide analogues are polymerase inhibitors. With respect to cell types treatable according to the precepts of the present invention, reference is made to the attached declaration of Dr. Au and the comments in the preceding paragraph. With respect to a nucleotide analog, reference is made to the application, wherein it is stated, *inter alia*:

> The term "nucleotide analog, or derivative thereof" refers to those art recognized modified nucleic acid bases that, typically, resemble a natural building block of DNA or RNA polymerization but have been modified to have an additional property such as, *e.g.*, the ability to inhibit a reverse transcriptase, *e.g.*, retroviral reverse transcriptases and telomerases.
>
> Application at page 11, ll. 32-36.

This definition certainly militates against the term being indefinite. Additional definitions of other analogs or derivatives and many other terms used in the application and claims are set forth in the definition section of the application at pp. 9-13. The data, Dr. Au's expert opinion, and the definitions in the application counter this claim rejection. Thus, its withdrawal respectfully is requested.

Claims 41 and 43 are rejected under 35 § U.S.C. 112, first paragraph, as not being enabling for identifying patients about to have cancer. The Examiner's attention respectfully is directed to the application, wherein it is stated, *inter alia*, that this term

> ...refers to a patient having been determined to have, or to be statistically likely to have, a cancer using various art recognized diagnostic or prognostic techniques including, *e.g.*, the PSA test, BRCA1 and/or BRCA2 genotyping, genetic profiling, *etc.* The term is also intended to include the mere knowing or receipt of any information (*e.g.*, a prognosis, diagnosis) indicating that the patient is having or about to have a cancer.
>
> Application at page 11, ll. 5-10

Thus, a definition of this term is set forth in the application. Indeed, the disputed term refers to patients that statistically are in a high-risk group to have cancer. Thus, it is not seen how this term is indefinite. Nevertheless, in order to materially advance prosecution of this application, the offending language has been removed from claims 41 and 43.

Claims 1-24, 26-28, 33-35, and 40-47 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject

matter which applicant regards as the invention due to the inclusion of the term, "telomere damage inducing agent". Initially, this term is defined in the specification:

> The term "telomere damage-inducing" refers to any measurable change to the end of a telomere when *e.g.*, compared to a control cell, chromosome, or nucleic acid and includes chromosomal fragmentation, telomere shortening, and the presence of DNA free ends.
>
> Application at page 12, ll. 23-26.

The term "telomere damage inducing agent" is enabled for an agent that causes damaged or shortened telomeres at a rapid onset, as described in Example 3; or prior to the initiation of apoptosis cascade, as described in Example 4. The term "telomere damage inducing agent" also refers to an agent that causes telomere damage, followed by a transient increase in telomerase activity, as described in Example 5. This term differs from "telomerase inhibitory agents", which are defined in the application as:

> The term "telomerase inhibitory agent" refers to an agent that inhibits (completely or partially) the activity of the enzyme telomerase.
>
> Application at page 12, ll. 27-29.

Thus, the term is not indefinite, as it has been defined in the application, and the term is different from "telomerase inhibitory agent", which similarly has been defined in the application. Nevertheless, in order to materially advance prosecution, the definitions in the Examples have been incorporated into claims 1 and 2. Again, no new matter is added by virtue of these claim amendments. Importantly, Applicants assert that no claims have been narrowed with the meaning of *Festo* (*Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 US 722, 112 S.Ct. 1831, 152 L.Ed.2d 944, 62 USPQ2d 1705 (2002)). See also *Interactive Pictures Corp. v. Infinite Pictures Inc.*, Fed Cir., No. 01-1029, December 20, 2001 (addition of the words "transform calculation" was not a narrowing amendment because that addition did nothing more than make express what had been implicit in the claim as originally worded).

102 (b) Claim Rejections Based on Gill

Claims 1-4, 8-10, 12-14, 16, 18, 20, 22-24, 26, 40, 42, and 44-46 stand rejected under 35 § U.S.C. 102(b) as being anticipated by Gill (U.S. Patent No. 5,756,537). Gill teaches that paclitaxel can be administered concurrently with AZT for the treatment of Kaposi's Sarcoma in patients with acquired immunodeficiency syndrome (AIDS).

This prior art in fact teaches that paclitaxel can be used to treat Kaposi's Sarcoma in AIDS patients who routinely received AZT and other reverse transcriptase inhibitors to manage the AIDS, but does not teach that adding AZT, d4T, or other reverse transcriptase inhibitors, through inhibition of telomerase, enhances the antitumor activity of paclitaxel. Hence, in the absence of the present invention, there is no motivation to use AZT, d4T or other reverse transcriptase inhibitors to enhance the telomere-directed effect of paclitaxel. Furthermore, the present invention enables the identification of an AZT treatment schedule to enhance the efficacy of paclitaxel, which cannot be found in the prior art, as the prior art does not provide guidance to finding such a treatment schedule. For example, the doses of AZT required for treatment of AIDS are higher compared to the AZT doses required to enhance the paclitaxel effect, as follows. The AZT doses used in AIDS patients are 100 mg every 4 hours given orally or 1 mg/kg given intravenously every 4 hours, given daily (PDR electronic library. Online version. Under Retrovir®). The present invention teaches that the synergy between paclitaxel and AZT is greatest when the dose ratio of AZT:paclitaxel is equal or less than 40:60 (see Example 8). Example 9 further shows that the intravenous AZT dose required to enhance the survival advantage of paclitaxel in tumor-bearing mice is 200 ng/hr/day. As the average weight of a mouse is about 20 g, this translates to 0.24 mg/kg/day. This dose is about 20-fold lower compared to the intravenous AZT dose of 5-6 mg/kg/day used to treat AIDS (PDR electronic library. Online version. Under Retrovir®). Claim 26 has been amended, and claims 91 and 92 have been added, to reflect the AZT doses and the ratios of AZT:paclitaxel concentrations discovered by the present invention.

§ 103(a) Rejection Based on Vande Woude in view of Merck Index

Claims 1-24, 26-28, 40, 42, and 44-47 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the Vande Woude (U.S. Patent No. 6,150,398), in view of The Merck Index, 1996, 7117,8958 and 1052. Vande Woude teaches that paclitaxel or a paclitaxel derivative can be used with an agent that effects the G1 or S phase of the cell division cycle. The Merck Index teaches that AZT and d4T are polymerase inhibitors, and that AZT has antiviral, antimetabolite, and antineoplastic activity. The Examiner proposes that polymerase inhibitors are often inhibitors of the G1 or S phase of cell division and, thereby, considers that the present invention is obvious based on combination of the prior art. However, Vande Woude did not define the AZT concentrations and doses that would affect the G1 or S phase of the cell division cycle. Chandrasekaren *et al.* showed that 50 to 200 micromolar AZT blocks cells in the G1/S phase (*Cancer Chemother Pharmacol* 35:489-495, 1995). The AZT dose required to produce 40 micromolar plasma concentration is 10 g/m2/day (Marchbanks *et al.*, *Pharmacotherapy*, 15:451-

457, 1995; Figure 1). Using a commonly accepted conversion factor of 37 kg/m2, the 10 g/m2/day dose equals about 270 mg/kg/day, which is about 1,000-fold higher than the 0.24 mg/kg/day AZT dose needed to produce synergy with paclitaxel. Furthermore, AZT is not known to have antiviral, antimetabolite, and antineoplastic activity at the low doses that enhance the antitumor activity of paclitaxel, as demonstrated in Example 9 in the present application (see the paragraph immediately below for detailed discussion). Hence, in the absence of the present invention, there is no motivation of combining paclitaxel and low dose AZT for the treatment of cancer or to use such low AZT doses.

The present invention on using d4T to enhance the efficacy of paclitaxel differs from the prior art in two respects. First, d4T does not always affect cells in the G1 or S phase. Li *et al.* shows that d4T arrests WiDr cells in the S phase but has no effect on MCF7 cells (Li *et al.*, *Anticancer Res* 17:21-28, 1997). This unpredictability in the art makes it unobvious to use d4T in combination with paclitaxel. Second, the present invention demonstrates that at least 20 micromolar d4T is needed to enhance the activity of paclitaxel, in view of Vande Woude. In comparison, the d4T concentration required to cause arrest of WiDr cells in the G1/S phase of the cell cycle is 10 micromolar (Li *et al.*). Accordingly, the present invention indicates the use of a 2-fold higher d4T concentration that the concentration that is needed to cause G1/S phase arrest. This d4T concentration requirement could not have been anticipated or made obvious by the Vande Woude publication. Claim 27 has been amended, and 90 has been added, to reflect the d4T concentration.

§ 103(a) Rejection Based on Melana in view of Merck Index

Claims 1-24, 26, 28, 40, 42, and 44-46 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the by Melana article, in view of the Merck Index. Melana teaches that AZT is effective in inhibiting the growth of four breast cancer cell lines and T4 cell leukemia, that AZT inhibits telomerase activity, and that AZT can be used, alone or in combination, as an anti-breast cancer agent. The Merck Index teaches that paclitaxel is a known antineoplastic for the treatment of breast of ovarian cancer.

The present invention is distinct from these earlier publications in several aspects. First, Melana teaches that AZT has antitumor activity at high concentrations; the 50% inhibitory concentrations of AZT were between 250 and 1,750 micromolar for the eight cell lines tested. In contrast, the present invention teaches using AZT to enhance the activity of paclitaxel, an effect that does not require AZT to have cytotoxic activity. Second, Melana teaches that inhibition of telomerase requires very high levels of AZT of between 500 to 2,000 micromolar AZT. In contrast, the present invention teaches using AZT at concentrations equal to or below 100

micromolar (see Example 8). Accordingly, Melana and the Merck Index do not teach using AZT together with paclitaxel, wherein the AZT concentration is equal to or below 100 micromolar. Third, although Melana suggests that AZT can be potentially used, alone or in combination, as an anti-breast cancer agent, the method of combining AZT with other drugs has not been explicitly disclosed. Several publications have described using AZT as antitumor agent, alone or in combination with other antitumor drugs (Marchbanks *et al.*, *Pharmacotherapy*, 15:451-457, 1995; Beitz et al., Cancer Investigation, 13:464-469, 1995; Posner et al, Cancer, 70:2929-2934, 1992; Posner *et al*, J. *Natl. Cancer Inst.*, 82:1710-1714, 1990). All these earlier studies used high doses of AZT, *i.e.*, between 2 to 20 g/m^2/day, and recommended a final dose of 7.5 g/m^2/day. Using the commonly accepted conversion factor of 37 kg/m^2, the 7.5 g/m^2/day dose is approximately 171 mg/kg/day. This AZT dose is about 680-fold higher than the 0.25 mg/kg/day AZT dose that enhances the efficacy of paclitaxel (see Example 9).

Fourth, Melana does not teach that the antitumor activity of AZT is due to telomerase inhibition. Melana states "the effect of AZT on other enzymes, such as DNA polymerase gamma and thymidine kinase, which are present in all cell types, cannot be ruled out" (p. 695, right column). Finally, telomerase is not considered a viable therapeutic target for cancer treatment (Huminiecki, *L. Acta Biochimica Polonica*, 43:531-538, 1996; Neidle and Kelland, *Anti-cancer Drug Design*, 14:341-347, 1999). Huminiecki states that "telomerase has not been usually considered to be a therapeutic target" (p.533, right column). Huminiecki further states "One can argue than even if such a (telomerase-targeting) therapy worked, its action would be very slow, and patients would probably die before telomeres of their malignant cells would shorten to a critical length" (p.534, left column). Neidle and Kelland state that "the emerging cellular biological properties of telomeres and telomerase as outlined above have caused some to question their validity as an anticancer target" (p. 342, first column). Hence, the use of telomerase inhibitor as described in the present invention is not obvioius based on the prior art. Further, the present invention, where AZT is used at doses of less than 170 mg/kg/day, cannot be obvious from the teaching of Melana, in view of the Merck Index. Claim 26 has been amended, and claims 91-92 have been added, to indicate the AZT dose or AZT concentrations identified by the present invention.

§ 103(a) Rejection Based on Melana in view of Merck Index and Pai

Claims 1-24, 26-28, 40, 42, and 44-47 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Melana in view of the Merck Index and Pai. Pai teaches that d4TTP inhibits telomerase in cell free extracts; 18% inhibition was achieved at 30 micromolar d4TTP. d4TTP is an intracellular metabolite of d4T. The prior art shows that incubation of human cells with 10

micromolar d4T yielded only 0.3 pmole of d4TTP per one million cells, indicating that only a very small percentage of d4T present in the extracellular fluid is converted to d4TTP its triphosphate metabolite (Zhu *et al.*, *Mol Pharmacol*, 40:838-845, 1991). There is no prior art to indicate the amount of intracellular d4TTP attained at 20-40 micromolar d4T in the extracellular matrix. A linear extrapolation based on the teaching of Zhu *et al.* and using the assumption that one million cells is approximately 1 microliter in volume, at least 1,000 micromolar extracellular d4T is required to yield 30 micromolar intracellular d4TTP. The 1,000 micromolar extracellular d4T concentration is at least 25-fold higher than the 20-40 micromolar extracellular d4T concentration used to improve the efficacy of paclitaxel, as is taught by the present invention. Accordingly, the present invention is not be rendered obvious by Melana, in view of Pai and the Merck Index. Claim 27 has been amended, and 90 has been added, to reflect the d4T concentration.

§ 103(a) Rejection Based on Gill in view of Merck Index

Claims 1-4, 7-28, 40, 42, and 44-47 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Gill, in view of the Merck Index. Gill teaches that paclitaxel can be administered concurrently with AZT to treat Kaposi Sacroma in AIDS patients, and that paclitaxel can be used with other antiretroviral agents that are used to treat AIDS. The Merck Index teaches that d4T is a reverse transcriptase inhibitor.

As discussed above, Gill does not teach using AZT to enhance the antitumor activity of paclitaxel and, therefore, does not teach how to find an AZT dose that can synergize with paclitaxel. In fact, Gill does not teach that any dose of AZT can synergize with paclitaxel. Hence, Gill does not render claims 1-4, 7-28, 33-35, and 40-47 unpatentable. The d4T doses used in AIDS patients are 60-80 mg per day (PDR electronic library. Online version. Under Zerit®). These doses would yield a maximum plasma concentration of about 4 micromolar (PDR electron library. Online version. Under Zerit®). The present invention teaches the synergy between paclitaxel and d4T where the d4T concentrations are at least 20 micromolar (see Example 8). This concentration is at least 5-fold higher compared to the concentration used to treat AIDS patients. Claims 26 and 27 have been amended, and claims 90-92 have been added, to reflect the distinguishing features of the present invention, regarding the AZT doses and concentrations, and the d4T concentrations.

Conclusion

In view of the amendments and remarks submitted herewith, allowance of the claims 1-24, 26-28, 33-35, 40-50, and 90-92 and passage to issue of this application respectfully are requested.

Respectfully submitted,

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